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UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

In re: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

Case No. 13-md-2452-AJB-MDD

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF DEFENDANTS' JOINT MOTION FOR SCHEDULING ORDER REGARDING CAUSATION

Date: February 18, 2014
Time: 9:00 a.m.

Judge: Hon. Anthony J. Battaglia
Courtroom: 3B

Magistrate: Hon. Mitchell D. Dembin

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PRELIMINARY STATEMENT

Merck Sharp & Dohme Corp. ("Merck"), Amylin Pharmaceuticals, LLC ("Amylin"), Eli Lilly and Company ("Lilly") and Novo Nordisk Inc. ("Novo") (collectively, "defendants"), respectfully request that the Court enter a scheduling order that takes up "general causation" expert discovery and related *Daubert* issues early in this litigation rather than waiting until the eve of a trial sometime late next year under Plaintiffs' proposed schedule for Amylin and Lilly or, in the case of Merck and Novo Nordisk, not until 2016 and 2017, respectively. Defendants further request the Court to order that, upon entry of an order for a schedule leading to a *Daubert* hearing on general causation, the parties meet and confer on discovery deadlines that would follow, if necessary, thereafter. In discussing a schedule, the parties have reached an impasse on which fork in the road this litigation should take: engage in expensive and time-consuming discovery on multiple issues for years or address a threshold issue within the next few months that could possibly determine the fate of this litigation without a needless expenditure of time and money. Once the Court directs the parties on which fork to take, the parties can seek to work out the balance of a schedule.

Nearly two months ago, on December 17, 2013, defendants proposed to plaintiffs a schedule to guide the management of this litigation. A copy of that proposal is attached as Exhibit A. In that schedule, defendants proposed that the plaintiffs have an additional three months beyond Science Day to submit expert reports setting out the basis for their claim that incretin-based therapies cause pancreatic cancer, a necessary element to their claim. Thereafter, defendants would submit their expert reports on general causation and the parties would engage in expert discovery, culminating in a *Daubert* hearing on this fundamental issue.

Last Monday evening, February 3, plaintiffs submitted their proposals for a schedule—one for Byetta, one for Januvia, and one for Victoza cases. Plaintiffs'

proposal set *Daubert* hearings shortly before trials, starting for Byetta late next year, 2015, and not occurring until 2016 and 2017 for Januvia and Victoza.

Rather than engage in a disconnected dialogue on a variety of issues where there is no alignment on the general framework for a schedule, defendants and plaintiffs agreed, with the Court's concurrence, to submit their respective positions to the Court on this threshold issue.

INTRODUCTION

This multidistrict litigation is quite different from the usual multidistrict litigation involving a prescription medication. Typically, the Judicial Panel on Multidistrict Litigation receives a request for pretrial coordination following the withdrawal of a medication from the market or, at least, the publication of a major study calling the medication's safety into question, with the consequent filing of hundreds of cases alleging a failure to warn of the risk. Think Diet Drugs (fen-phen), Vioxx, Celebrex, Bextra, Propulsid, Rezulin, Baycol, Phenylpropranolamine (PPA), Prempro, Trasylol—the list goes on.

In the ordinary case, "general causation"—that is, whether a medication is *capable* of causing the alleged harm—is often an important threshold issue in pharmaceutical litigation. However, that issue is often overshadowed by issues related to the warning and to "specific causation"—whether a medication caused a particular plaintiff's harm. "Typical" litigations follow typical discovery schedules that address general causation discovery and *Daubert* after the completion of generic fact discovery.

But the story is different for the incretin-based therapies that are the subject of this MDL. Causation is the critical issue here. None of the products has been withdrawn from the market. No study in humans or animals has concluded that these medicines increase the risk of pancreatic cancer. Nor has any observational study so concluded.

What is so different about the incretin-based therapies, as compared to the prescription medications in earlier MDLs, is a combination of three things: (1) there is a wealth of scientific data about these medicines; (2) the scientific community has reached a consensus that there is no sound scientific evidence that the medications cause pancreatic cancer; and (3) that consensus is current. Indeed, there were at least four expressions of that consensus in 2013:

- In July 2013, after convening a special task force to study the scientific data, the European Medicines Agency ("EMA"), Europe's equivalent to the FDA, announced in a comprehensive seventeen-page report that "[c]oncerning pancreatic cancer, there is currently ***no support*** from clinical trials that GLP-1 based therapies increase the risk."[1] In a press release, the EMA announced that "presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines."[2]
- The Food and Drug Administration said the following week that it "concurs" with the EMA and that the EMA's assessment reflects the FDA's current understanding of the science, as well.[3]
- In June 2013, the National Institute of Diabetes and Digestive and Kidney Diseases ("NIDDK") and the National Cancer Institute ("NCI") convened a first-ever joint conference of leading experts in the fields of diabetes and pancreatic cancer.[4] Afterwards, the American Diabetes Association, European Association for the Study of Diabetes, and the International Diabetes Federation issued a joint statement about the conference (i) explaining that the FDA

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[1] European Medicines Agency [EMA], *Assessment report for GLP-1 based therapies*, at 16, EMA Doc. 474117/2013 (July 25, 2013) ("EMA Report") (attached as Ex. 17) (emphasis added).

[2] Press Release, European Medicines Agency, *Investigation into GLP-1 based diabetes therapies concluded: No new concerns for GLP-1 therapies identified on the basis of available evidence* (July 26, 2013) (attached as Ex. 18).

[3] Ed Silverman, *Diabetes Drugs Pancreatic Cancer Risk Not Backed By Existing Evidence: FDA*, Pharmalot (July 31, 2013), https://web.archive.org/web/20130819002506/http://www.pharmalive.com/fda-decides-no-risk-of-pancreatic-cancer-with-diabetes-drugs (attached as Ex. 37).

[4] *See* NIDDK-NCI Workshop on Pancreatitis-Diabetes-Pancreatic Cancer (June 12–13, 2013), http://www2.niddk.nih.gov/News/Calendar/PDPC2013.htm (last visited Feb. 4, 2014).

presented a thorough review of the animal data "finding ***no concerns for pancreatic disease***" and (ii) recommending the incretin-based therapies for their "equivalence, if not superiority" to other antidiabetic medications.[5]

- In August 2013, the American Association of Clinical Endocrinologists and the American College of Endocrinology issued a Consensus Statement concluding that for incretin-based therapies there is "***[n]o evidence*** of . . . pancreatic cancer in humans."[6]

Thus, the experts directly concerned with the regulation of incretin-based therapies and the experts directly concerned with the treatment of diabetes and pancreatic cancer have recently reviewed the body of scientific data evaluating the potential relationship between the therapies and pancreatic cancer, and they have determined that the data do not support the presence of an association, much less a causal relationship.

So, on what sound scientific basis do plaintiffs rely for disagreeing with the European Medicines Agency, the FDA, the American Diabetes Association ("ADA"), the European Association for the Study of Diabetes ("EASD"), the International Diabetes Federation ("IDF"), the American Association of Clinical Endocrinologists and the American College of Endocrinology? If this litigation were to proceed on a routine path, the answer to this fundamental question would not be known for years.

The Court has the discretion—and good cause to exercise it—to have this question answered now, based on the evidence currently available. Doing so will "promote[] judicial efficiency [and] prevent[] the potential waste of the parties' and the Court's resources." *In re Viagra Prods. Liab. Litig.*, MDL No. 1724, slip op. at 1 (D. Minn. June 30, 2006) (attached as Ex. 47). Amylin, Lilly, Merck, and Novo

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[5] ADA/EASD/IDF Statement Concerning the Use of Incretin Therapy and Pancreatic Disease (June 28, 2013), http://www.diabetes.org/newsroom/press-releases/2013/recommendations-for.html (emphasis added) ("ADA/EASD/IDF Statement") (attached as Ex. 1).

[6] *See* Yehuda Handelsman, et al., *Diabetes and Cancer – An AACE/ACE Consensus Statement*, Endocrine Practice, 19(4):675 (2013), at 685, 687 (emphasis added) (attached as Ex. 24).

Nordisk request the Court to exercise that discretion to enter a discovery schedule that addresses "general causation" expert discovery and related *Daubert* issues at the outset of this MDL.

There is nothing to lose, and everything to gain, by this approach. General causation discovery is underway and can be completed quickly. Virtually all of the evidence that real-world scientists rely on to make general causation determinations is publicly available. To the extent that defendants are in possession of non-public data, it either has been produced already or can be produced in short order. *Daubert* hearings on general causation can proceed soon thereafter. At that point, if the Court finds—like U.S. and European organizations—that there is no reliable basis to establish causation in this case, the litigation will conclude, "sav[ing] thousands of person-hours and millions of dollars [that would have been spent on] unnecessary efforts." *In re Agent Orange Prod. Liab. Litig.*, 506 F. Supp. 762, 796–97 (E.D.N.Y. 1980). If not, the case nevertheless will have been advanced considerably, resolving a key issue common to all cases, at no extra cost to the parties or the Court.

By contrast, if this litigation takes the path plaintiffs prefer, the dissonance between plaintiffs' allegations and the state of the science will endure for years. Under the plaintiffs' proposals, the parties and the Court would not take up general causation—concerning Byetta only—until August 2015, on the eve of the first trial. Whether or not Victoza and Januvia can cause pancreatic cancer would not be addressed until 2 ½ years and 3 years from now, respectively. Meanwhile, the parties and the Court will embark on a long and expensive journey involving the production of millions of pages of documents and the taking of scores of depositions, with legal skirmishes along the way over a variety of issues. Then, only after spending untold amounts of time, money, and judicial resources on discovery and procedural wrangling, would the Court turn to whether there is a sound scientific basis for plaintiffs' claims and whether the litigation should proceed to bellwether trials.

This process takes a toll, and not just in time and money spent on litigation. Patients who take the medications, but are subjected to litigation-driven advertisements or accounts in the media about risks of the medications, may be left uneasy. And doctors may be less willing to prescribe the medications, even though they remain FDA-approved and despite the guidance from the ADA, EASD and IDF that incretin-based therapies are "equivalen[t], if not superior[]" to other antidiabetic medications, lest they be drawn into the litigation as parties or witnesses.[7]

Checking speculative science at the gate "help[s] assure that the powerful engine of tort liability, which can generate strong financial incentives to reduce, or to eliminate, production, points toward the right substances and does not destroy the wrong ones." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 148–49 (1997) (Breyer, J., concurring).[8] As we explain further below, the Court is endowed with "broad discretion to tailor discovery narrowly and to dictate the sequence of discovery . . . to facilitate [the] prompt and efficient resolution of the lawsuit." *Crawford-El v. Britton*, 523 U.S. 574, 598–99 (1998). Under the circumstances presented here, legal precedent and principles of effective case management make it appropriate to exercise that discretion to put the general causation question first in this case:

- First, the *Manual for Complex Litigation* encourages "sequencing and limitations" on discovery, and "tak[ing] up early in the litigation" issues such as

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[7] ADA/EASD/IDF Statement (Ex. 1).

[8] *See also Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 677–78 (6th Cir. 2010) (citing media reports "describing how scientists concluded, after years of litigation, billions in settlements and the bankruptcy of a major manufacturer, that no evidence tied breast implants to health problems"); Gina Kolata, A Case of Justice, or a Total Travesty?; How the Battle Over Breast Implants Took Dow Corning to Chapter 11, N.Y. Times (June 13, 1995), *available at* http://www.nytimes.com/1995/06/13/business/case-justice-total-travesty-battle-over-breast-implants-took-dow-corning-chapter.html.

"whether the facts and expert evidence support a finding that the products . . . have the capacity to cause the type of injuries alleged."[9]

- Second, causation is an essential element of every claim. Other MDL courts have structured discovery to address causation as a threshold issue. This is fully consistent with plaintiffs' obligation to have a good-faith basis for alleging causation "***before*** filing their claims."[10]
- Third, a scientific hypothesis, as distinguished from reliable scientific evidence, will not meet that obligation. As one MDL court observed, "Medical science may one day determine with sufficient reliability that a causal relationship exists . . . but it is not there yet and may never be. A trial court must function in the present ***assessing evidence that presently exists***."[11]
- And, finally, discovery on general causation can be accomplished quickly and at little cost to the parties. Most, if not all, of the information necessary for plaintiffs to make their general causation case is in the public domain or has been produced to them already. There is nothing to lose, and everything to gain, by taking up this threshold issue first, rather than requiring the Court and the parties to delve into expensive discovery on issues that may not be necessary.

MEDICAL BACKGROUND

Byetta, Januvia, and Victoza have all been approved by FDA for the treatment of type 2 diabetes, a disease characterized by chronic high levels of blood sugar. They are broadly referred to as "incretin-based therapies" because they increase levels of certain incretin hormones which help lower blood sugar by stimulating production of insulin. Incretin-based therapies have become an important treatment option for patients with type 2 diabetes and continue to be recommended by all leading medical organizations in the diabetes field.[12]

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[9] *Manual for Complex Litigation (Fourth)* ("*Manual*"), § 11.211, at 38, § 22.634, at 411 (2004).

[10] *Acuna v. Brown & Root, Inc.*, 200 F.3d 335, 340 (5th Cir. 2000) (emphasis added).

[11] *In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 615 (E.D. La. 2003) (emphasis added) (citation omitted).

[12] *See* ADA/EASD/IDF Statement (Ex. 1).

These medications work very differently from one another, however, having different mechanisms of action, different pharmacology, different methods of administration, different clinical and preclinical data profiles, and different labels. Broadly speaking, Byetta and Victoza are injectable, synthetic analogs of the incretin hormone GLP-1and mimic the effects of natural GLP-1 in the body. They are known as GLP-1 Receptor Agonists. Januvia, by contrast, is a DPP-4 inhibitor. It extends the life of naturally occurring incretin hormones (like GLP-1) by inhibiting the DPP-4 enzyme, which otherwise would operate to disable or "turn off" the incretin hormones.[13]

In this MDL, plaintiffs allege that one or more incretin-based therapies caused them to develop pancreatic cancer. As the Court learned during Science Day, pancreatic cancer is an insidious disease. It is the fourth leading cause of cancer death in the United States and once diagnosed, patients have a one-year survival rate of about 20 percent, and a five-year survival rate of less than 5 percent.[14] This is because pancreatic cancer develops slowly and generally lacks symptoms until it is in an advanced stage. Indeed, by the time it is usually diagnosed, a person will have been on the path to cancer for twenty years or more, and will have had pancreatic cancer for more than ten years.[15] This is a critical point given that the first incretin-based therapy, Byetta, has only been on the market since 2005. In addition, diabetes and

[13] The differences between DPP-4 inhibitors and GLP-1 Receptor Agonists are meaningful. In its recent report on the safety of incretin-based therapies, the EMA stressed that future evaluations "should be done in a product specific manner . . . considering differences in mechanism of action (i.e. GLP-1 receptor agonists [such as Byetta and Victoza] versus DPP-4 inhibitors [such as Januvia] . . . ." EMA Report at 17.

[14] Irene Chong & David Cunningham, *Pancreatic Cancer, in Harrison's Principles of Internal Medicine* (Dan L. Longo, et al., eds., 18th Ed. 2012) (attached as Ex. 10); Jan-Bart Koorstra, et al., *Pancreatic Carcinogenesis*, Pancreatology, 8:110 (2008), at 110 (attached as Ex. 28).

[15] Shinichi Yachida, et al., *Distant metastasis occurs late during the genetic evolution of pancreatic cancer*, Nature, 467:1114 (2010) (attached as Ex. 44).

pancreatic cancer are deeply interrelated. Diabetes is a serious risk factor for pancreatic cancer. Approximately 50 to 80 percent of all pancreatic cancer patients have diabetes at the time they are diagnosed.[16] Likewise, undiagnosed pancreatic cancer can also cause diabetes—that is, diabetes can be a symptom of the cancer before the cancer is known to exist.

ARGUMENT

This multidistrict litigation is different from other pharmaceutical MDLs. None of the products at issue in this case has been withdrawn from the market. There is no study—preclinical or clinical—that demonstrates that any of the products cause the alleged harm, pancreatic cancer. Indeed, in the months leading up to the establishment of this MDL, U.S. and European regulators, along with the scientific community, concluded that there is no evidence that these products do what plaintiffs claim. Rather, these products have been deemed safe and remain a critical part of the battle against the diabetes epidemic.

The Federal Rules provide the Court with the discretion to meet these unique circumstances with a tailored solution. And while it is rare at the outset of pharmaceutical litigation for there to be a broad consensus that the medications at issue are safe, it is by no means unprecedented to address general causation first to promote efficiency and the conservation of resources.[17] Indeed, it makes eminent

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[16] YunFeng Cui & Dana Andersen, *Diabetes and pancreatic cancer*, Endocrine-Related Cancer, 19:F9 (2012) (attached as Ex. 11); Feng Wang, et al., *The relationship between diabetes and pancreatic cancer*, Molecular Cancer; 2:4 (2003) (attached as Ex. 42).

[17] *See, e.g.*, *In re Viagra Prods. Liab. Litig.*, MDL No. 1724, slip op. at 1 (D. Minn. June 30, 2006) (limiting first phase of discovery to general causation and holding early *Daubert* hearing) (attached as Ex. 47); *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, MDL No. 1407, slip op. at 1 (W.D. Wash. Mar. 22, 2002) (setting schedule for expert discovery within first few months after MDL was formed) (attached as Ex. 46); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, MDL No. 1699, slip op. at 1–4 (N.D. Cal. Mar. 16, 2007) (ordering early expert discovery and *Daubert* hearings regarding plaintiffs' experts' causation opinions)

sense to give priority to discovery on the potentially dispositive threshold issue of general causation.[18] Taking up general causation "early in the litigation" is an approach recommended by the *Manual for Complex Litigation*. *Manual for Complex Litigation* § 22.634, at 411. For the reasons described below, the Court should do so here. There is no downside.

I. The Scientific Consensus Is that There Is No Reliable Evidence that the Incretin-Based Therapies Cause Pancreatic Cancer.

In their Master Complaint, the plaintiffs point to various studies, conducted largely by one group of academic researchers led by Dr. Peter Butler from UCLA. A closer examination of these studies reveals, however, that they do not support the plaintiffs' contentions:

- The first publication—an editorial, not a study—by Dr. Peter Butler and his team, was published in February 2010 and offers nothing more than a hypothesis that GLP-1 based therapy "may" increase the risk of pancreatitis (inflammation of the pancreas).[19] The strongest language that the Complaint can quote from the Butler article is: "We ***feel*** that enough ***preliminary*** evidence has accumulated to ***suggest*** that there is a ***plausible*** risk that long-term recipients of GLP-1 based therapy ***may*** develop asymptomatic pancreatitis [ ], and worse, subsequently a minority of individuals treated by this class of drugs ***may*** develop pancreatic cancer."[20] This hedged conclusion falls far short of a reasonable degree of scientific certainty.[21]

(attached as Ex. 45); *see also In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166 (N.D. Cal. 2007).

[18] *See Crawford-El*, 523 U.S. at 599–600.

[19] *See* Master Compl. ¶¶ 43–44 (Dkt. No. 206); Peter C. Butler, et al., *GLP-1-Based Therapy for Diabetes: What You Do Not Know Can Hurt You*, Diabetes Care; 33(2):453 (2010), at 455 (attached as Ex. 9).

[20] *See* Peter C. Butler, et al., *GLP-1-Based Therapy for Diabetes: What You Do Not Know Can Hurt You*, Diabetes Care, 33(2):453 (2010), at 453–54 (Ex. 9).

[21] *See Kilpatrick v. Breg, Inc.*, No. 08-10052-CIV, 2009 WL 2058384, at *7 (S.D. Fla. June 25, 2009) (finding editorial written by expert was "to say the least,

And, indeed, Butler and his colleagues did not purport to claim that their work established causation.[22]

- The second[23] and third reports[24] cited in the Master Complaint[25] are based on materially limited analyses of spontaneous adverse event reports. Both reports acknowledge that they are fundamentally limited due to their reliance on spontaneous adverse event reports ("AERS") collected by the regulators. Although important to the FDA's monitoring of drug safety, the FDA expressly cautions that AERS data cannot support statistical conclusions of causation:[26] the data is inherently unreliable and incomplete and the databases are subject to proven bias arising from, among other things, attorney advertising and case filings. The courts have held repeatedly that adverse-event data cannot support a conclusion about causation.[27]

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inadequate as a basis for a scientific judgment about the general causation"), *aff'd*, 613 F.3d 1329 (11th Cir. 2010).

[22] *See Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 468 (E.D. Pa. 2008) ("In cases where no adequate study shows the link between a substance and a disease, expert testimony will generally be inadmissible, even if there are hints in the data that some link might exist."); *Bickel v. Pfizer, Inc.*, 431 F. Supp. 2d 918, 924 (N.D. Ind. 2006) (rejecting causation theory purportedly based on published medical literature where the literature merely "'proposed' a connection").

[23] Michael Elashoff, et al., *Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies*, Gastroenterology, 141:150 (2011) (attached as Ex. 13).

[24] Arzneimittelkommission der deutschen Ärzteschaft (Drug Commission of the German Medical Association - AkdÄ), *Pancreatic cancers associated with exenatide (Byetta®)*, German Medical Journal; 108(19):1080 (2011) (attached as Ex. 4).

[25] *See* Master Compl. ¶¶ 45–54.

[26] *See* FDA Adverse Event Reporting System (FAERS) (formerly AERS), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[27] *See, e.g.*, *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1250 (11th Cir. 2005); *In re Zicam Cold Remedy Mktg., Sales Practices, & Prods. Liab. Litig.*, No. 09-md-2096-PHK-FJM, 2011 WL 798898, at *10–11 (D. Ariz. Feb. 24, 2011); *In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1041 (D. Minn. 2007); *DeLuca ex rel. DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1051 (D.N.J. 1992) (adverse event reports "are not of a type of data that are reasonably relied upon by experts in the fields of epidemiology and public health to make a determination of

- The Master Complaint also cites hypothesis-generating studies in animals that are rebutted by the majority of the science and, critically, that scientists have been unable to reproduce.[28] The consensus in the scientific community is that these studies do not create a safety concern. In these studies—one that treated just 16 rats with Januvia,[29] and two others that treated just 10 and 15 rats with Byetta[30, 31]—researchers reported that incretin-based therapies were associated with an increased incidence of pancreatitis and histomorphological changes to the exocrine pancreas. None of these animals developed pancreatic cancer. Moreover, these findings conflict with studies performed on thousands of animals to support the approval of these medicines,[32] as well as recent studies that were unable to replicate the findings using larger numbers of animals and longer exposures to Januvia,[33] Victoza,[34] and Byetta.[35]

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the causal relationship between a given substance and human birth defects"); *Nelson v. Am. Home Prods. Corp.*, 92 F. Supp. 2d 954, 969 (W.D.Mo.2000) (adverse event reports are not proof of causation).

[28] *See* Master Compl. ¶¶ 56–60.

[29] Aleksey Matveyenko, et al., *Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin*; Diabetes 58:1604–1615 (2009) (attached as Ex. 30).

[30] J.S. Nachnani, et al., *Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas*, Diabetologia 58:1604–1615 (2009) (attached as Ex. 33).

[31] Belinda Gier, et al, *Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras^{G12D} mouse model*, Diabetes, 61(5): 1250-1262 (2012) (attached as Ex. 22).

[32] Tim Hummer, Acting Supervisory Toxicologist, Division of Metabolism and Endocrinology Products, U.S. Food & Drug Administration, Presentation on FDA Surveillance of Adverse Drug Effects (June 13, 2013) (attached as Ex. 27) (reviewing data from over 250 studies involving more than18,000 animals).

[33] *See, e.g.*, Katheryn Aston-Mourney K, et al., *One year sitagliptin treatment protects against islet amyloid-associated β-cell loss and does not induce pancreatitis or pancreatic neoplasia in mice,* Am. J. Physiol. Endocrinol. Metab 305:E475–E484 (2013) (attached as Ex. 5); Thomas Forest, et al., *Characterization of the Exocrine Pancreas in the Male Zucker Diabetic Fatty Rat Model of Type 2 Diabetes Mellitus*

- Finally, the Master Complaint[36] relies on a study in which the Butler group examined the pancreases of eight brain dead organ donors who had been treated with incretin-based therapies and purported to find that those subjects had increased pancreatic mass and pancreatic α-cell hyperplasia.[37] Independent experts have rejected this study for its serious methodological flaws, including the failure to properly match treated and untreated subjects and omission of important confounding data on the subjects that was readily available.[38] As described below, the European Medicines Agency expressly rejected Dr. Butler's study for its unsound scientific basis.

Significantly, what the Master Complaint does not cite is the most recent analysis of the evidence by the same group of researchers which concluded that, while there is a "plausible mechanism" based on animal data to infer "a potential risk of pancreatic

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Following 3 Months of Treatment with Sitagliptin, Endocrinology (2014) (attached as Ex. 20).

[34] N. Vrang, et al., *The effects of 13 wk of liraglutide treatment on endocrine and exocrine pancreas in male and female ZDF rats: a quantitative and qualitative analysis revealing no evidence of drug-induced pancreatitis*, Am. J. Physiol. Endocrinol. Metab.; 303:E253-E264 (2012) (attached as Ex. 41).

[35] K. Tatarkiewicz, et al., *No evidence of drug-induced pancreatitis in rats treated with exenatide for 13 weeks*, Diabetes, Obesity & Metabolism (2012) (attached as Ex. 38).

[36] *See* Master Compl. ¶¶ 72–75.

[37] Alexandra Butler, et al., *Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors*, Diabetes 62:2595–2604 (2013) (attached as Ex. 7).

[38] Evis Harja, et al., *An Analysis of Characteristics of Subjects Examined for Incretin Effects on Pancreatic Pathology*, Diabetes Technology & Therapeutics 15:609 (2013) (concluding "that the data and the implications of the data . . . are vastly overstated and seemingly irresponsibly articulated" and that the "irresponsible indictment of two classes of drugs that are used by millions of people . . . is reprehensible") (attached as Ex. 25); Susan Bonner-Weir, et al., *Re-analysis of study of pancreatic effects of incretin therapy: Methodological deficiencies*, Diabetes, Obesity & Metabolism (2014) ("the data presented in the Butler paper have serious methodological deficiencies that preclude any meaningful conclusions") (attached as Ex. 6).

cancer," the "case presented here does not prove that these agents are unsafe." Peter C. Butler, et al., *A Critical Analysis of the Clinical Use of Incretin-Based Therapies: Are GLP-1 therapies safe?*, Diabetes Care (published online ahead of print May 6, 2013) (attached as Ex. 8).

Arrayed against the reports cited in the Master Complaint are the conclusions reached by the principal scientific bodies concerned with incretin-based therapies, diabetes, and pancreatic cancer. Within the past year, these independent scientific bodies have evaluated the possible association between the therapies and pancreatic cancer. This includes all of the data that plaintiffs purport to rely on to allege causation. And these independent bodies have concluded, overwhelmingly, that the evidence does not support a causal link between incretin-based therapies and pancreatic cancer.

The EMA Report (July 2013). In 2013, the European Medicines Agency reviewed all of the preclinical (animal) and clinical (human) data on incretin-based therapies, and convened a group of distinguished experts to consider the safety of the incretin-based therapies "further to the findings by a group of academic researchers [the Butler group] suggesting an increased risk of pancreatitis and cellular changes in patients treated for [Type-2 diabetes] with GLP-1 based therapies."[39] The EMA specifically evaluated Dr. Butler's organ donor study,[40] then thoroughly reviewed and summarized the preclinical and clinical data for each incretin-based therapy "with a focus on pancreatitis and/or pancreatic cancer."

The EMA reached and published the following conclusions:

- "With respect to nonclinical data, ***available studies previously submitted for the approved products have not raised concern with respect to pancreatic***

[39] EMA Report at 13.

[40] Alexandra Butler, et al., *Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors*, Diabetes 62:2595–2604 (2013) (Ex. 7).

safety. Further, published studies have not shown any evidence for treatment-related pancreatitis or preneoplastic [i.e., pre-cancerous] lesions . . . ."

- "Concerning pancreatic cancer, ***there is currently no evidence from clinical trials that GLP-1 based therapies increase the risk***."
- "[T]he randomized, controlled nature of the clinical studies gives a robust estimate of risk in relation to placebo and other treatments. ***The data currently available from clinical trials do not indicate an increased risk for pancreatic cancer with these medicines***."[41]

The EMA also found that the Butler organ donor study was not well-designed or conducted, and that the data did not support even its tentative conclusions.[42] In its assessment report, the EMA explained in detail the Butler study's flaws and said by way of summary:

- "Overall the experts considered that ***there was a high number of methodological issues, confounding factors and potential sources of bias in the Butler et al 2013 publication*** and that ***these precluded any meaningful conclusions*** to establish a link between GLP-1 based therapies and morphological changes of the pancreas indicating an increased risk of pancreatic malignancies."
- "Overall, the experts considered that the presented evidence did ***not*** support the view that GLP-1 based therapies resulted in histological changes of the pancreas in these individuals indicating an increased risk of pancreatic adenocarcinoma."[43]

The EMA Report is the most current and comprehensive review of the scientific data concerning incretin-based therapies and pancreatic cancer.[44]

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[41] EMA Report at 15, 16.

[42] As noted above, Dr. Butler does not assert that the incretin medicines increase the risk of pancreatic cancer. Peter C. Butler, et al., *A Critical Analysis of the Clinical Use of Incretin-Based Therapies: Are GLP-1 therapies safe?*, Diabetes Care (published online ahead of print May 6, 2013) (Ex. 8).

[43] EMA Report at 11, 17.

[44] The EMA report acknowledges that pancreatic cancer is rare and may not be detected in clinical or even observational studies and, therefore, further study is

The FDA. The FDA recently stated that it concurs with the EMA's findings, has completed its own review of the data (including for over 18,000 animals studied during the preclinical development and postmarketing analysis of incretin-based therapies), has conducted its own animal studies, and is drafting its own report. An FDA spokeswoman said that "the agency believes that the current labeling for approved GLP-1 based therapies reflects the extent of our understanding of the safety signals at this point in time."[45]

The American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation, NCI, and NIDDK. In June 2013, the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases convened a joint conference of leaders in the fields of diabetes and pancreatic cancer.[46] The conference addressed whether there is evidence that incretin-based therapies cause pancreatic cancer. The FDA made a presentation. Following the NCI/NIDDK conference, the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation issued a joint statement:

> A June 2013 NIH workshop reviewed the epidemiologic associations between diabetes and pancreatic carcinoma . . . . The FDA presented a thorough review of the pre-clinical pathology from submissions of all [incretin-based therapies]

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warranted. But, as the EMA recognizes, scientific conclusions must be drawn from current data and the current data does not support a causal link between incretin-based therapies and pancreatic cancer. Similarly, the law mirrors good science. As explained in Part II, the law is clear that a litigant must rely on the science as it is, and not how it might—or might not—be. Allegations about causation must be based on data and not simply act as a placeholder in the hope that other scientific evidence might materialize someday.

[45] Ed Silverman, *Diabetes Drugs Pancreatic Cancer Risk Not Backed By Existing Evidence: FDA*, Pharmalot (July 31, 2013) (Ex. 37).

[46] *See* NIDDK-NCI Workshop on Pancreatitis-Diabetes-Pancreatic Cancer (June 12–13, 2013), http://www2.niddk.nih.gov/News/Calendar/PDPC2013.htm.

> on the market and under development, and three additional submissions requested, ***finding no concerns for pancreatic disease***.[47]

The ADA, EASD, and IDF all affirmed their recommendation of incretin-based therapies as an important option for treating diabetes.

Endocrinologists. On August 20, 2013, the American Association of Clinical Endocrinologists and the American College of Endocrinology issued a Consensus Statement on the relationship between diabetes and cancer. The organizations acknowledged Dr. Butler's "speculations about the theoretical possibility of increased incidence of pancreatic cancer" arising from incretin-based therapies, but concluded that the risk has not been proven. "[N]o randomized controlled prospective human study of [incretin-based therapies] has conclusively shown that these drug classes play a role in the genesis of pancreatic cancer," the statement noted, and it summarized the data in these words: "No evidence of . . . pancreatic cancer in humans."[48]

Randomized Clinical Trial Data. The "gold standard" for assessing general causation is randomized clinical trial data. *Reference Manual on Scientific Evidence* 555 (Fed. Judicial Ctr. 3rd ed. 2011); *see also id.* at 729 ("Well-performed randomized [clinical] trials provide the least biased estimates of treatment benefit and harm by creating groups with equivalent progress.").[49] The randomized clinical trial data for Januvia, Byetta, and Victoza do not show an increased risk of pancreatic cancer in patients taking incretin-based therapies.[50] Indeed, currently there are more than 80,000 patients enrolled in large-scale clinical trials of cardiovascular safety of

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[47] ADA/EASD/IDF Statement (Ex. 1).

[48] Yehuda Handelsman, et al., *Diabetes and Cancer – An AACE/ACE Consensus Statement*, Endocrine Practice; 19(4):675 (2013), at 686, 687 (Ex. 24).

[49] *See also In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1172–73 (N.D. Cal. 2007).

[50] Summaries of the clinical, observational, and animal data for Januvia, Victoza, and Byetta are set forth in detail in Exhibits B, C, and D, respectively.

incretin-based therapies. These studies are evaluated by independent Data Safety Monitoring Boards, which have the ethical responsibility to terminate the trial if there are safety concerns. The trials for Byetta, Victoza, and Januvia are monitoring pancreatic cancer events and none has been terminated for a safety concern. Two trials for other incretin-based therapies were completed in late 2013. Their results were published in the *New England Journal of Medicine*.[51] Neither trial found evidence of an increased pancreatic cancer risk. Indeed, for the DPP-4 inhibitor saxagliptin, there were five incidences of pancreatic cancer in the treatment group and twelve in the group that received a placebo. For alogliptin, no pancreatic cancer was reported.

Observational Studies. Observational studies using healthcare databases and similar sources can provide important information regarding the safety of medications under real world conditions. Although less favored than randomized clinical trial data because they have fewer controls, observational studies can also provide insights into causation.[52] Observational studies of Januvia, Byetta, and Victoza currently canvass more than 75,000 patient-years of exposure to these medications. None of these studies found evidence that these products increase the risk of pancreatic cancer.

Studies in Animals. Animal studies generally cannot prove causation in and of themselves.[53] Here, however, the animal studies align with the observational and randomized clinical data. The defendants all conducted extensive animal toxicity and carcinogenicity studies as part of the approval process and as part of their

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[51] *See* Scirica, et al., *Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus*, New England J. of Medicine 369:14;1317 (2013) (attached as Ex. 36); White, et al., *Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes*, 369:14;1327 (2013) (attached as Ex. 43).

[52] *See Reference Manual on Scientific Evidence* 555.

[53] *See Reference Manual on Scientific Evidence* 23; *see also Domingo ex rel. Domingo v. T.K.*, 289 F.3d 600, 606 (9th Cir. 2002); *Daubert v. Merrell Dow Pharm., Inc. (Daubert II)*, 43 F.3d 1311, 1315 (9th Cir. 1995); *In re Silicone Gel Breast Implants Prods. Liab. Litig.*, 318 F. Supp. 2d 879, 890 (C.D. Cal. 2004).

postmarketing obligations; none demonstrated that the incretin-based therapies increase the incidence of pancreatic cancer. In addition, at the request of the FDA, the manufacturers conducted studies to evaluate the pancreatic effects of their incretin-based therapies in diabetic rats. None of these studies found evidence of adverse pancreatic effects, negating the outlying rat studies performed by the Butler group, described above.

II. The Federal Rules and Principles of Sound Judicial Management Favor Ordering Structured Discovery Addressing General Causation First.

This litigation is the quintessential case for the consideration of causation early in the litigation—before millions of dollars and substantial resources are spent on other issues. Recent, systematic, and consensus-setting reviews of the available science by neutral experts have produced a near-unanimous view that there is no sound scientific basis on which to conclude that there is a causal link between incretin-based therapies and pancreatic cancer.[54] General causation is a "pivotal" issue that may "provide the foundation for a dispositive motion." *Manual for Complex Litigation*, § 11.422, at 54–55 (2004). Addressing it first has the potential to "preempt[] the need for almost all of the discovery" that would otherwise be undertaken. *In re Agent Orange Prod. Liab. Litig.*, 506 F. Supp. 762, 796–97 (E.D.N.Y. 1980).

[54] *See Allen v. Pennsylvania Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996) (affirming judgment as a matter of law where "not a single scientific study has revealed a link between human brain cancer and EtO exposure" and "numerous reputable epidemiological studies covering in total thousands of workers indicate there is not a correlation between EtO exposure and cancer of the human brain").

A. Principles of Sound Judicial Management

Rule 16 authorizes the Court to exercise "early and continuing control" to discourage wasteful pretrial activities and to expedite disposition of the case.[55] Rule 26 gives the Court "broad discretion to tailor discovery . . . to facilitate prompt and efficient resolution of the lawsuit."[56] The Ninth Circuit recognizes that "administering cases in multidistrict litigation is different" from administering cases on a routine docket.[57] This is "a special breed of complex litigation where the whole is bigger than the sum of its parts."[58] In such cases, the case management order governing the schedule for the litigation takes on even greater importance.

As the Court knows, the *Manual for Complex Litigation* is replete with advice about steps that the Court can take early in the case to narrow the issues, avoid unnecessary expense, and speed resolution. *The Manual* advises the Court to:

- "[A]nticipate[] problems before they arise" and "become[] familiar at an early stage with the substantive issues in order to make informed rulings on issue definition and narrowing";[59]
- "[P]ress the parties to identify, define and narrow the issues," starting at the initial conference;[60]
- "[R]equir[e], with respect to one or more issues, that the parties present a detailed statement of their contentions, with supporting facts and evidence";[61]

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[55] *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 460 F.3d 1217, 1227 (9th Cir. 2006) ("Rule 16, the central pretrial rule, authorizes a court to manage cases so that disposition is expedited, wasteful pretrial activities are discouraged, the quality of the trial is improved, and settlement is facilitated. It recognizes the need for adopting special procedures for managing potentially difficult or protracted actions that may involve complex issues, multiple parties, difficult legal questions, or unusual proof problems. The goal is to get cases decided on the merits of issues that are truly meritorious and in dispute" (internal quotation marks and citation omitted.)).

[56] *Crawford-El*, 523 U.S. at 598–99.

[57] *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 460 F.3d at 1229.

[58] *Id.* at 1232.

[59] *Manual* § 10.13, at 12.

[60] *Id.* § 11.31, at 42.

- Recognize that "[e]arly and full disclosure of expert evidence can help define and narrow issues";[62] and
- Include within the "[i]ssues to be taken up early in the litigation . . . whether the facts and expert evidence support a finding that the products . . . in question have the capacity to cause the type of injuries alleged."[63]

The circumstances here warrant the early exploration of whether there is a scientific basis to proceed, or whether the law should follow the scientific consensus that there is not. The Court should follow the example of other MDL courts that have structured discovery to put general causation and *Daubert* first.[64]

There is no cost to addressing general causation first. Most of the information that plaintiffs require to make their general causation case to the Court—studies and other scientific data—is published and is publicly available.[65] This is the same

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[61] *Id*. § 11.33, at 46.

[62] *Id*. § 11.481, at 99.

[63] *Id*. § 22.634, at 411.

[64] *See, e.g.*, *In re Viagra Prods. Liab. Litig.*, MDL No. 1724, slip op. at 1 (D. Minn. June 30, 2006) (limiting first phase of discovery to general causation and holding early *Daubert* hearing); *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, MDL No. 1407, slip op. at 1 (W.D. Wash. Mar. 22, 2002) (setting schedule for expert discovery within first few months after MDL was formed); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, MDL No. 1699, slip op. at 1–4 (N.D. Cal. Mar. 16, 2007) (ordering early expert discovery and *Daubert* hearings regarding plaintiffs' experts' causation opinions); *see also In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166 (N.D. Cal. 2007); *Avila v. Willits Envl. Remediation Trust*, 633 F.3d 828, 836 (9th Cir. 2011) (requiring plaintiffs to make a *prima facie* showing of general causation before commencing full blown discovery); *Claar v. Burlington Northern R.R.*, 29 F.3d 499, 500 (9th Cir. 1994) (Where there is "concern that plaintiffs might not be able to demonstrate a causal connection," case management orders should be used to require plaintiffs to "explain the scientific basis" for their claims).

[65] *See e.g.*, *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 143–47 (1997) (evaluating admissibility of general causation testimony based on epidemiologic and animal studies); *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311 (9th Cir. 1995) (evaluating admissibility of expert testimony based on epidemiologic studies, animal

information that the scientific community relies on to make its determinations. Further, defendants have already produced to plaintiffs all of their correspondence and submissions to FDA through late 2013. These include data from internal preclinical and clinical studies, investigator statements, responses to requests for information from FDA, study protocols, adverse event reports, other safety reports, and annual reports. If plaintiffs lack something they genuinely need to establish their general causation case, defendants can produce it without undue delay. *Daubert* can follow soon after.

No matter the outcome, early resolution of the general causation question will advance the ultimate objective of the MDL process—the resolution of issues common to all cases. If plaintiffs cannot produce reliable expert testimony to support their general causation claims, defendants will have grounds for summary judgment. If, on the other hand, the Court finds that plaintiffs' experts' opinions on general causation are based on reliable science, the issue will have been resolved, the parties will have gained valuable information about the cases, and both the Court and the parties can move on to other issues.

B. Early General Causation Discovery Does Not Alter Plaintiffs' Burden

A discovery plan that takes up general causation first would shift the default order of discovery but would not alter the burden that plaintiffs undertook when they commenced this litigation in spite of the broad consensus that the products at issue do not cause pancreatic cancer. The Federal Rules of Civil Procedure require a plaintiff "to 'stop and think' before initially making . . . factual contentions," because a complaint constitutes a certification that the "factual contentions have evidentiary

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studies, and chemical analogy); *Lopez v. Wyeth-Ayerst Labs., Inc.*, 139 F.3d 905, 905 (9th Cir. 1998) (unpublished table decision) (evaluating admissibility of expert testimony based on epidemiologic studies, animal studies, and adverse event reports); *In re Bextra & Celebrex*, 524 F. Supp. 2d at 1176–83 (evaluating admissibility of general causation testimony based on observational studies, clinical trial data, and a biological plausibility theory).

support."[66] What is true for all factual contentions is arguably true *a fortiori* for contentions as to scientific causation. The law is clear that a plaintiff who has only a scientific hypothesis and lacks reliable scientific evidence of causation cannot put his case to the jury. *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1178 (E.D. Wash. 2009) ("Evidence that is an insightful hypothesis is not admissible in court if it lacks scientific rigor."); *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996) ("[T]he courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it."). Thus, a plaintiff who has not identified reliable scientific evidence of causation before filing suit has not made the reasonable inquiry required by the Rules. *Acuna*, 200 F.3d at 340 (plaintiffs must have had *prima facie* valid basis for asserting causation before filing claims).[67]

Put differently, both the Rules of Civil Procedure and the Rules of Evidence are concerned with what is true ***now***. Speculation about scientific studies as yet unconducted and scientific data as yet uncollected and unreported cannot satisfy the duty to base allegations on a reasonable inquiry into the facts. Nor can such speculation constitute the substance of expert testimony. "Though Plaintiffs' theory may one day be validated through scientific research and experiment, the law ***today*** cannot apply that conjecture." *Henricksen*, 605 F. Supp. 2d at 1178 (emphasis added).

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[66] Fed. R. Civ. P. 11(b) & advisory committee notes, 1993 amendments.

[67] *See also In re Vioxx Prods. Liab. Litig.*, 557 F. Supp. 2d 741, 744 (E.D. La. 2008) (same); *In re Silica Prods. Liab. Litig.*, 398 F. Supp. 2d 563, 675 (S.D. Tex. 2005) (awarding sanctions where law firm brought cases without basis for causation); *Lore v. Lone Pine*, 1986 WL 637507, at *3 (N.J. Super. Ct. Law Div. Nov. 18, 1986) ("preliminary expert reports should have been obtained prior to filing suit"); *Martinez v. City of San Antonio*, 40 S.W.3d 587, 591 (Tex. App. 2001) (upholding causation order, remarking that "[plaintiffs] are presumed to have duly investigated their case before filing suit"); *In re Love Canal Actions*, 547 N.Y.S.2d 174, 177 (N.Y. Sup. Ct. 1989) (requiring showing of causation, noting that "New York requires attorneys in all actions to investigate the legal and factual basis for an action before commencing litigation").

In short, lawsuits are not fishing expeditions, and, more specifically, a plaintiff may not allege causation as a placeholder for supporting scientific evidence that the plaintiff only hopes will materialize in the future. The Rules permit discovery—sometimes wide-ranging, voluminous, and very expensive discovery—but only when the initial allegations have demonstrable current "evidentiary support." The law asks whether such evidence exists ***now***.[68]

* * *

This litigation presents circumstances that warrant early inquiry by the Court into whether plaintiffs can prove causation. There is no reason to proceed with years of expensive, full-scale document and deposition discovery if there is no *Daubert*-worthy scientific data that support the allegation that incretin-based medicines cause pancreatic cancer. That plaintiffs may have a hypothesis about causation will not suffice. Nor will it suffice that plaintiffs may hope that future studies will reach different conclusions.[69] MDL coordination is meant to expedite the resolution of complex litigation, not serve as a holding pen. "[T]he law cannot wait for future scientific investigation and research. We must resolve cases in our courts on the basis of scientific knowledge that is currently available." *Moore v. Ashland Chem. Inc.*, 151

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[68] *See Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002) ("courts may only admit the state of science as it is . . . not . . . speculation, conjecture, or inference that cannot be supported by sound scientific principles"); *In re Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644, 690 (D.N.J. 2008) ("The Rules of Evidence, however, cannot be disregarded even if at a future date, medical and scientific literature proves the contrary."); *In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 615 (E.D. La. 2003) ("The Court is aware that the future may shed more light on this matter. Medical science may one day determine with sufficient reliability that a causal relationship exists between a sustained prolonged QT interval and Propulsid but it is not there yet and may never be. A trial court must function in the present assessing evidence that presently exists." (citation omitted)).

[69] *See, e.g.*, *Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 381 (5th Cir. 2010); *Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 276 (5th Cir. 1998); *In re Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644, 690 (D.N.J. 2008); *In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 615 (E.D. La. 2003).

F.3d 269, 276 (5th Cir. 1998). Therefore, the Court should adopt a scheduling order that addresses "general causation" expert discovery at the outset, requires plaintiffs to produce general causation expert reports, in compliance with Rule 26, and sets dates for *Daubert* briefing on causation in this litigation. The schedule defendants proposed does just that.

Dated: February 10, 2014 Respectfully Submitted,

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SIGNATURE ATTESTATION

Pursuant to Section 2.f.4 of the Court's CM/ECF Administrative Policies, I hereby certify that authorization for the filing of this document has been obtained from each of the other signatories shown above and that all signatories have authorized placement of their electronic signature on this document.

By: s/ Vickie E. Turner
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LIST OF EXHIBITS
DEFENDANTS' SUBMISSIONS

SUPPORTING AUTHORITIES

8.	Peter C. Butler, et al., *A Critical Analysis of the Clinical Use of Incretin-Based Therapies: Are GLP-1 therapies safe?*, Diabetes Care (published online ahead of print May 6, 2013)	**110-118**
9.	Peter C. Butler, et al., *GLP-1-Based Therapy for Diabetes: What You Do Not Know Can Hurt You*, Diabetes Care; 33(2):453 (2010)	**119-122**
10.	Irene Chong & David Cunningham, *Pancreatic Cancer, in Harrison's Principles of Internal Medicine* (Dan L. Longo, et al., eds., 18th Ed. 2012)	**123-129**
11.	YunFeng Cui & Dana Andersen, *Diabetes and pancreatic cancer*, Endocrine-Related Cancer, 19:F9 (2012)	**130-148**
12.	Dore DD, et al. Incidence of Health Insurance Claims For Thyroid Neoplasm and Pancreatic Malignancy in Association With Exenatide: Signal Refinement Using Active Safety Surveillance. *Therapeutic Advances in Drug Safety.* 2012;3(4):157-164	**149-158**
13.	Michael Elashoff, et al., *Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies*, Gastroenterology, 141:150 (2011)	**159-166**
14.	Samuel Engel et al., *Safety and Tolerability of Sitagliptin in Type 2 Diabetes: Pooled Analysis of 25 Clinical Studies*, Diab. Therapy (published online May 23, 2013)	**167-194**
15.	Samuel Engel et al., *Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis*, Int'l J. of Clinical Practice, 64:984 (2010)	**195-202**
16.	D. Eurich et al., *Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes: retrospective population based cohort study*, British Med. J., 346:f2267 (2013)	**203-213**
17.	European Medicines Agency [EMA], *Assessment report for GLP-1 based therapies*, EMA Doc. 474117/2013 (July 25, 2013)	**214-231**
18.	Press Release, European Medicines Agency, *Investigation into GLP-1 based diabetes therapies concluded: No new concerns for GLP-1 therapies identified on the basis of available evidence* (July 26, 2013)	**232-234**
19.	Exenatide Periodic Safety Update Report for 01 October 2008 through 31 March 2009	**235-238**
20.	Thomas Forest, et al., *Characterization of the Exocrine Pancreas in the Male Zucker Diabetic Fatty Rat Model of Type 2 Diabetes Mellitus Following 3 Months of Treatment with Sitagliptin*, Endocrinology (2014)	**239-250**

21.	D. Funch et al., *A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs*, Diabetes, Obesity and Metabolism 2013; doi:10.1111/dom.12230	**251-254**
22.	Belinda Gier, et al, *Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras^{G12D} mouse model*, Diabetes, 61(5): 1250-1262 (2012)	**255-268**
23.	M. Gokhale et al., *Dipeptidyl Peptidase 4 Inhibitors and Comparative Pancreatic Cancer Risk Among Older Adults*, Abstract presented at June 2013 NIDDK/NCI conference	**269-270**
24.	Yehuda Handelsman, et al., *Diabetes and Cancer – An AACE/ACE Consensus Statement*, Endocrine Practice, 19(4):675 (2013)	**271-290**
25.	Evis Harja, et al., *An Analysis of Characteristics of Subjects Examined for Incretin Effects on Pancreatic Pathology*, Diabetes Technology & Therapeutics 15:609 (2013)	**291-301**
26.	Hiles R, et al. Exenatide Does not Cause Pancreatic Tumors or Malignancies in Rats and Mice Following a 2-Year Period of Exposure. Presented at 64th Scientific Session of the American Diabetes Association (2004)	**302-303**
27.	Tim Hummer, Acting Supervisory Toxicologist, Division of Metabolism and Endocrinology Products, U.S. Food & Drug Administration, Presentation on FDA Surveillance of Adverse Drug Effects (June 13, 2013)	**304-310**
28.	Jan-Bart Koorstra, et al., *Pancreatic Carcinogenesis*, Pancreatology, 8:110 (2008)	**311-328**
29.	Steven Marso et al., *Design of the liraglutide effect and action in diabetes: Evaluation of cardiovascular outcome results (LEADER) trial*, Am. Heart J. 2013;166:823-830.e5	**329-342**
30.	Aleksey Matveyenko, et al., *Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin*; Diabetes 58:1604–1615 (2009)	**343-355**
31.	Matteo Monami, *et al.*, *Dipeptidyl Peptidase-4 Inhibitors and Pancreatitis Risk*, Diabetes, Obesity & Metabolism; 16:48–56 (published online July 9, 2013)	**356-365**
32.	Moore TJ et al. QuarterWatch Monitoring MedWatch Reports.	**366-382**
33.	J.S. Nachnani, et al., *Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas*, Diabetologia 58:1604–1615 (2009)	**383-390**

34.	Niels Nyborg et al., *The Human GLP-1 Analog Liraglutide and the Pancreas Evidence for the Absence of Structural Pancreatic Changes in Three Species*, Diabetes 2012;61:1243-1249	**391-398**
35.	Romley JA, et al. Exenatide Therapy and the Risk of Pancreatitis and Pancreatic Cancer in a Privately Insured Population. *Diabetes Technol & Ther.* 2012;14(10):904-911	**399-407**
36.	Scirica, et al., *Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus*, New England J. of Medicine 369:14;1317 (2013)	**408-418**
37.	Ed Silverman, *Diabetes Drugs Pancreatic Cancer Risk Not Backed By Existing Evidence: FDA*, Pharmalot (July 31, 2013)	**419-423**
38.	K. Tatarkiewicz, et al., *No evidence of drug-induced pancreatitis in rats treated with exenatide for 13 weeks*, Diabetes, Obesity & Metabolism (2012)	**424-434**
39.	Tatarkiewicz K et al. Exenatide Does Not Evoke Pancreatitis and Attenuates Chemically Induced Pancreatitis in Normal and Diabetic Rodents. *Am J Physiol Endocrinol Metab* 2010;299:E1076-E1086	**435-446**
40.	Victoza FDA Summary Review, Application 22-341 (January 25, 2013)	**447-512**
41.	N. Vrang, et al., *The effects of 13 wk of liraglutide treatment on endocrine and exocrine pancreas in male and female ZDF rats: a quantitative and qualitative analysis revealing no evidence of drug-induced pancreatitis*, Am. J. Physiol. Endocrinol. Metab.; 303:E253-E264 (2012)	**513-526**
42.	Feng Wang, et al., *The relationship between diabetes and pancreatic cancer*, Molecular Cancer; 2:4 (2003)	**527-532**
43.	White, et al., *Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes*, 369:14;1327 (2013)	**533-542**
44.	Shinichi Yachida, et al., *Distant metastasis occurs late during the genetic evolution of pancreatic cancer*, Nature, 467:1114 (2010)	**543-549**
45.	*In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, MDL No. 1699, slip op. at 1–4 (N.D. Cal. Mar. 16, 2007)	**550-561**
46.	*In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, MDL No. 1407, slip op. at 1 (W.D. Wash. Mar. 22, 2002)	**562-564**
47.	*In re Viagra Prods. Liab. Litig.*, MDL No. 1724, slip op. at 1 (D. Minn. June 30, 2006)	**565-574**